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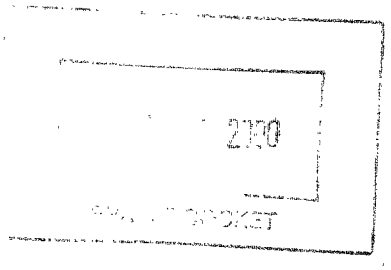
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
RESEARCH TRIANGLE PARK, NC 27711

MEMORANDUM

OFFICE OF
AIR QUALITY PLANNING
AND STANDARDS

DATE: October 21, 1999

SUBJECT: Comments on MEK manuscript



FROM: William K. Boyes
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TO: Gary Foureman
NCEA

At your request we have evaluated a manuscript entitled "Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone and cyclohexanone" by Mitran et al., (1997) in connection with a proposal to remove methyl ethyl ketone (MEK) from the Clean Air Act list of Hazardous Air Pollutants.

Mitran et al (1997) report the study of solvent workers and matched controls from three Romanian factories. The subjects were exposed to either acetone, MEK or cyclohexanone. Evaluations of the workers included symptom questionnaires, a clinical evaluation and nerve conduction velocity. Nerve conduction testing was performed on the median and ulnar nerves of the arm of the dominant hand and the peroneal nerve of the ipsilateral leg. The results reported include increased frequencies of a variety of symptoms, including for MEK approximately a three-fold increase in the percentage of workers reporting numbness of the hands or feet. Workers exposed to cyclohexanone and acetone reported similar or greater increases in this symptom. Nerve conduction velocity was reported to be decreased in all three sets of workers. Measures on the conduction of each nerve tested included the latency, amplitude and duration of the response after stimulating from proximal and distal sites, in addition to calculating nerve conduction velocity. For MEK, statistically significant increases were reported for 15 of 21 measures of nerve conduction. The authors of the study caution against over interpretation of the results of nerve conduction measures, yet recommended that the occupational exposure limits of each of the three compounds be lowered on the basis of these results.

A critical appraisal of the study by Mitran et al (1997) reveals several shortcomings and concerns. First, very few methodological details are presented making it virtually impossible to determine what was done. It is not clear what factors were "matched" when the control groups were selected and how comparable the groups were on factors other than age, which appears to have been well matched. Factors that could be important but are not mentioned include things

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like type of work (e.g. office vs physical work), lifestyle factors (drinking, smoking etc) and height and weight (important for nerve conduction). Experimental procedures are also unspecified including whether the subjects were tested at the same location and time as the exposed workers, and whether the examiners were aware of the exposure status of the subjects at the time of testing. Importantly, the control of temperature, a critical factor in nerve conduction studies, was not mentioned. A valid interpretation of the nerve conduction results might be that the controls were tested in a hotter environment than the exposed workers.

It is also important to evaluate the pattern and consistency of the results obtained. The pattern of nerve conduction results is not entirely consistent with a peripheral neuropathy. For MEK (their Table 7) significant increases in latency were seen for the proximal and distal latencies for the median and ulnar nerve, but only for the proximal latency for the peroneal nerve. Distal axonopathies of the type caused by chemicals similar to MEK, such as methyl-n-butyl ketone (MnBK) or n-hexane, produce earlier and more severe damage in the distal ends of the longest and largest diameter nerve fibers. Thus, in a peripheral neuropathy one would expect the distal latency of the peroneal nerve to be the most altered of the latencies measured, and not the sole spared value. There are other inconsistencies that also tend to reduce confidence in the data. For example, in the peroneal nerve the latency, and not the amplitude, of the proximal response is altered but the amplitude, and not the latency, of the distal response is altered. It is difficult to conceive of a biological explanation for these contrary results.

The reports of increased numbness of the hands or feet in the exposed workers are consistent with what would be expected in a peripheral neuropathy, however this finding is based on self-reported symptoms of the workers and is not supported by any objective evaluation of sensory perception in these sites. A correlation between nerve conduction measures and self reports of sensory problems would also have increased the confidence in these outcomes if it was shown that those complaining of symptoms also had poor electrophysiological findings. Similarly, confidence would be increased if they had broken down the exposed group by individual exposure levels and showed a dose-response relationship. No analysis like this was presented.

Of primary importance is a consideration of the extent to which this report is supported by the other existing scientific literature. In this regard the report is most suspect. The peripheral axonopathy produced by n-hexane, MnBK and similar compounds is one of the best understood of the chemical-induced neurotoxicities (see review articles by Spencer et al, 1980; Anthony and Graham 1991). It is clear that compounds with a 6-carbon chain and a 1,4(γ) spacing of carbonyl groups (referred to as γ-diketones), or compounds that are metabolic precursors of γ-diketones, lead to a neurofilamentous axonopathy. The animal models of this condition are excellent predictors of human neuropathy. MEK has been well tested for this condition and is convincingly negative. Likewise exposure to acetone, also implicated by the Mitran paper, is not associated with peripheral axonopathy. In this regard the paper by Mitran et al is not consistent with a large volume of high quality neurotoxicological scientific evidence.

There is good evidence in the scientific literature, however, that exposure to MEK can

potentiate the neuropathy caused by co-exposure to n-hexane or MnBK (Spencer et al, 1980). This occurs, presumably, through competition for a metabolic detoxification pathway. Therefore it is good practice to avoid co-exposure to MEK and neuropathic γ-diketones. Note that hexane (CAS 110-54-3) is also listed as a HAP by the clean air act.

In conclusion, the paper by Mitran et al (1997) presents too little methodological information for a critical appraisal, presents results that are in some cases inconsistent with a peripheral neuropathy, and presents results that are discrepant with a large amount of scientific evidence that MEK is not associated with peripheral neuropathy. We do not recommend making this paper a consideration in determining whether or not MEK should continue to be listed on the HAP list. That decision is best made on other grounds. One of the consideration might be the possibility for co-exposure to hexane, for which MEK potentiates the toxicity.

References

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